Quality by Design (QbD) Position for Acryl-EZE® Film Coatings

Executive Summary

Colorcon has many years of experience in coating system development and manufacture which led to the creation of best-in-class fully formulated products such as the Acryl-EZE®, Aqueous Enteric System. This document outlines Colorcon's process for ensuring the quality and consistency of all Acryl-EZE systems, including Acryl-EZE II.

Film coating using a fully formulated coating system is highly beneficial with reduced or no risk to drug product development, manufacture, and performance. As Colorcon strictly controls the raw material quality and color in the manufacture of its fully formulated film coatings, they are not considered to be a critical risk factor in Quality by Design (QbD) when conducting a holistic risk assessment.

This document discusses the various controls to guarantee acceptable and repeatable product performance.

Acryl-EZE Technology Overview

Acryl-EZE is a fully-formulated film coating for oral solid dosage forms, which is designed to prevent release of active substances in acidic media of the stomach but then allow complete release at higher pH in the small intestine (about pH 5.5). This delayed release functionality is dependent upon the film coating formulation, the amount of coating applied and the coating process parameters selected.

Film Coating Formulation

The enteric film-forming polymer in the Acryl-EZE formulation is EUDRAGIT® L 100-55, an Evonik product. EUDRAGIT L 100-55 has pH dependent solubility, being insoluble in acidic media but soluble above a pH of about 5.5. To enhance dispersion in water and coating characteristics, Acryl-EZE is formulated with an alkalizing agent, a plasticizer, a detackifier and other additives. Colorcon optimized the Acryl-EZE formulations through a series of Design of Experiments (DOEs).

Amount of Film Coating Applied

During the development of Acryl-EZE, Colorcon extensively investigated the effect of coating level on the release characteristics of various oral solid dosage forms. For simplicity, and after confirming high process efficiencies, the amount of film coating applied to the substrate is generally expressed as theoretical percentage weight gain. For standard tablets and capsules (100-1,000 mg total weight), theoretical weight gains of about 7-10% W/W are required to ensure reproducible delayed release performance. For multiparticulates, theoretical weight gains of 20-50% W/W are often required due to the increased surface area relative to standard tablets and capsules.

A seal-coat may be required to separate alkaline drugs from the enteric polymer or to strengthen the dosage form prior to enteric coating.

Coating Process Parameters

The quality of film formation and process efficiency are greatly influenced by the process parameters selected. Optimal process parameters vary by coating equipment type and scale; however, Colorcon has conducted coating process DOEs to develop starting point coating process recommendations. Please consult the following references for further information.

Coating Parameters for the Use of Acryl-EZE®

Coating Parameters for the Use of Acryl-EZE® MP

Optimal Coating Process Parameters for a Fully Formulated, Acrylic-Based, Enteric, Film Coating System

QbD Considerations

For delayed release oral solid dosage forms, one universal Critical Quality Attribute (CQA) is the drug release profile. Though the exact nature of the drug release profile (duration of acid resistance, pH trigger point for release, rate of release above the pH trigger point) may vary amongst drug products, it is essential that the release profile be consistent within established limits to ensure efficacy of the drug. In its Q8(R2) Pharmaceutical Development Guidance for Industry, the International Conference on Harmonization (ICH) recommended that a risk assessment linking material attributes and process parameters to drug products CQAs be conducted. The following table summarizes the formulation and process variables that may influence the drug release profile for delayed release oral solid dosage forms and how the use of Acryl-EZE impacts the risk assessment.

Formulation and Process Variables	Risk Assessment when Using Acryl-EZE	Explanation
Core/multiparticulates formulation apart from coating	Medium	Largely independent of Acryl-EZE use. May need a seal-coat if a basic API is selected or a friable core is developed.
Delayed release coating formulation	Low	Acryl-EZE formulations were optimized using DOEs to perform reproducibly and are manufactured by Colorcon using tight manufacturing tolerances on component levels (ingredient weighing must be within ± 0.01 kg regardless of batch size). Colorcon also has tight quality controls on incoming raw materials and release specifications on Acryl-EZE formulations.
Amount of film coating applied	Low-Medium	Need to be established for drug formulation on case by case. Then it should be controllable if coating equipment has good process controls. End-users must decide the target and acceptable range of coating weight gain for a given product.
Coating process	Low-Medium	Colorcon developed its recommended coating process parameters based on DOEs, and these should be a good starting point to establish the process parameters for end-users' coating equipment. Since end-users' equipment and scale may vary, it is important that the optimal parameters be verified/established on their own equipment.

Batch-to-Batch Variability of Acryl-EZE Products

Any batch-to-batch variation which has the potential to influence any performance characteristics of Acryl-EZE is minimized by the use of strict controls in the production cycle.

- Starting materials are purchased from approved suppliers according to specifications based on both regulatory pharmacopoeial requirements and application specific requirements. Compliance with these specifications is verified prior to use.

- Starting materials are dispensed to a pre-set tight tolerance and then each batch of product is manufactured according to formula-assigned work instructions, with designated critical steps being countersigned.
- Prior to final product release each batch is subject to relevant Quality Control testing, which includes homogeneity of blending alongside enteric disintegration performance. Final release is completed by the Quality Assurance function following a full batch review of all manufacturing processes.

Summary

By selecting Acryl-EZE as the film coating for a delayed release product, Colorcon simplifies the control strategy by providing a consistent, tightly-controlled product of high quality that can be considered as low risk in QbD risk assessments based on substantial prior knowledge.

ICH Q8 (R2) recommends that a control strategy be developed to ensure that a product of required quality be produced consistently. Colorcon can assist end-users to reduce the risk of the corresponding coating process by helping to develop optimal coating levels and process parameters also based on our prior knowledge.

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